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Esophageal Granular Cell Tumor: A Benign Tumor or an Insidious Cause for Concern?

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Background: Esophageal granular cell tumors (GCTs) are rare, often benign tumors of neurogenic origin. GCTs most frequently occur in the skin and subcutaneous tissues but are found in the gastrointestinal (GI) tract in 6%-10% of cases, with the distal two-thirds of the esophagus being the most common site. Owing to the insidious nature of GCTs, presentation is typically asymptomatic. In fact, GCTs are often discovered incidentally during investigation of other GI disturbances.

Case Report: We report the case of a 36-year-old white male who had a 2.3 × 2.0-cm submucosal mass of the midesophagus found during esophagogastroduodenoscopy (EGD) at an outside hospital for workup of chronic diarrhea. He was referred to us for further evaluation that led to a diagnosis of a large esophageal GCT.

Conclusion: Because of the rarity of GCTs in clinical practice and their poorly defined malignant classification, proper workup and management are essential to avoid the potential morbidity and mortality associated with large and/or malignant tumors. Although malignancy is uncommon, approximately 1%-2% of esophageal GCTs are malignant. Conservative management is tolerated for benign, asymptomatic lesions <10 mm in diameter, but endoscopic removal is recommended for large, symptomatic tumors or those with features suggestive of malignancy. Routine surveillance often includes EGD and/or esophageal ultrasonography to evaluate tumor size, location, and depth and to exclude malignancy or lymph node involvement.

Keywords: *Esophageal neoplasms, granular cell tumor, neoplasms*

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INTRODUCTION

First described by Abrikossoff in 1926, granular cell tumors (GCTs) are rare tumors that occur in various parts of the body.[1] Formerly known as myoblastomas or Abrikossoff tumors, GCTs most frequently occur in the skin and subcutaneous tissues.[1,2] Less commonly, they are observed in the thyroid, respiratory tract, female urogenital tract, nervous system, breast, and gastrointestinal (GI) tract.[1,2] Tumors in the GI tract represent only 6%-10% of all GCTs, with the esophagus being the most common site in 30%-60% of these cases.[1,3] These neoplasms are often solitary in nature, with 10% of reports describing multifocal lesions.[4] Although their clinical course is relatively benign, approximately 2% of GCTs are malignant.[4]

CASE REPORT

A 36-year-old white male with a history of hypertension, sarcoidosis, diabetes, and end-stage renal disease who was on dialysis presented with chronic diarrhea. He reported no fevers, chills, weight loss, bloody stools, nausea, vomiting, dysphagia, or chest pain. Esophagogastroduodenoscopy (EGD) at an outside hospital revealed a midsized 2.3 × 2.0-cm submucosal lesion of the midesophagus (Figure 1). The lesion was nonobstructing, noncircumferential, and without evidence of bleeding. The patient was referred to us for further workup and management. Endoscopic ultrasonography (EUS) with fine-needle aspiration (FNA) demonstrated a round, intramural (subepithelial) lesion in the middle one-third of the esophagus, 35 cm from the incisors and extending to 37 cm. It was 19 mm in thickness with well-defined endoscopic borders. The mass was hypoechoic and originated from the deep mucosa with submucosal involvement. We observed no evidence of parenchymal invasion to the muscularis propria or periesophageal lymphadenopathy. Concurrent FNA revealed abundant spindle cells. Final pathologic diagnosis was confirmed by immunohistochemistry (IHC) that showed the mass to be positive for S100 (Figure 2) and CD68 (Figure 3) and negative for CKIT (CD117) and actin. Figures 2 and 3 show spindling. These findings are consistent with a diagnosis of an esophageal GCT.

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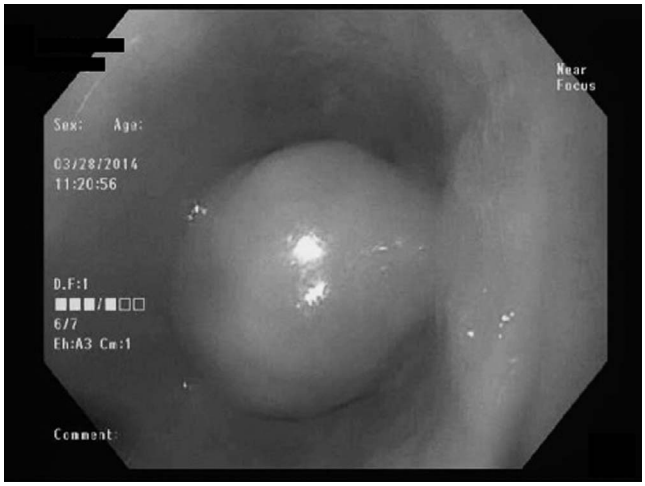

Figure 1. Endoscopy demonstrates the classic submucosal pill appearance of a pinkish mass covered by normal-appearing mucosa.

A follow-up EUS at 3 months showed no significant changes. Endoscopic submucosal dissection or endoscopic mucosal resection will be considered if the mass becomes symptomatic or develops features concerning for malignant transformation. Otherwise, the patient will return for endoscopy yearly or if symptoms develop. His diarrhea was self-limiting and unrelated to the GCT.

DISCUSSION

Esophageal GCTs are uncommon tumors of neurogenic origin, thought to arise from Schwann cells to form part of the esophageal submucosal neuronal plexus.[1] They were first described in the tongue in 1926 by Abrikossoff but later reported in the esophagus in 1931.[1,4] Despite the esophagus being the most common location for GI GCTs, esophageal GCTs remain quite rare. The distal one-third of the esophagus is the most common location in 65% of cases, while occurrence in the middle or proximal thirds is less common at 20% and 15%, respectively.[5]

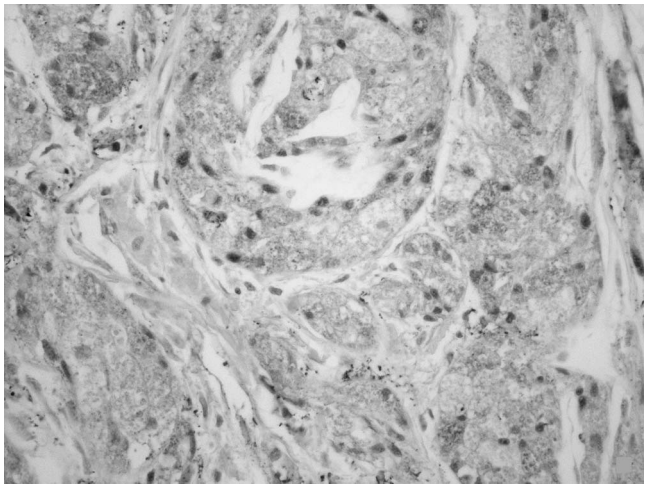

Figure 2. Immunohistochemistry of the mass from fine-needle aspiration demonstrates S100+ cell block at ×40 magnification. Note the presence of spindling.

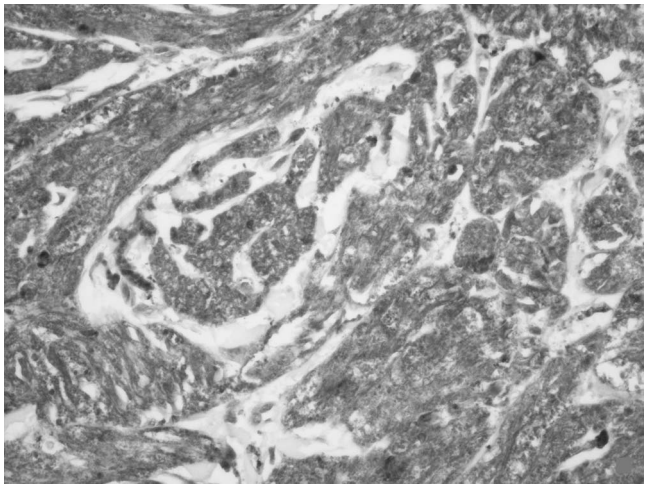

Figure 3. Immunohistochemistry of the mass from fine-needle aspiration demonstrates CD68+ cell block at ×40 magnification. Note the presence of spindling.

Esophageal GCTs commonly occur during the fourth to sixth decades of life, with some reports indicating a slight predilection for the female sex.[1,3] The tumors are typically insidious in nature, with most patients being asymptomatic at the time of diagnosis. In fact, GCTs are often encountered as incidentalomas in the investigation of other GI disturbances. When tumors are symptomatic, patients most commonly have complaints of retrosternal pain and discomfort.[3] Less commonly reported symptoms include epigastric pain, nausea, or vomiting.[3] Unsurprisingly, these symptoms have a linear correlation to lesion size, with lesions <20 mm in diameter often remaining asymptomatic.[3]

Owing to the rarity of GCTs in clinical practice, more common differential diagnoses must be considered when investigating an esophageal mass: leiomyoma, GI stromal tumor, esophageal cyst, rhabdomyoma, schwannoma, melanoma, hamartoma, squamous papilloma, squamous cell carcinoma, and metastasis.[1-3] Thorough workup to establish a correct diagnosis is paramount and traditionally includes imaging with both EGD and EUS.

EGD demonstrates the classic appearance of an esophageal GCT as a submucosal pill, a yellow-gray, intramural lesion with a firm to hard consistency covered by normal-appearing mucosa.[3] EUS plays an important role in both diagnosis and management of esophageal GCTs. EUS is invaluable in determining tumor size, location, depth of invasion, and origin of the lesion and in excluding malignancy and/or lymph node involvement.[3,5,6] The typical finding on EUS is a hypoechoic, homogeneous, and smooth-margined tumor within the mucosa or submucosa.[5] Approximately 95% of esophageal GCTs occur within the mucosa, with the remaining 5% occurring in the submucosa,[4] and in rare cases, within the muscularis propria, as described in two cases reported by Chen et al.[5] Together, both endoscopy and EUS can readily differentiate GCTs from malignant lesions, esophageal cysts, inflammatory polyps, and lipomas.[5] Esophageal leiomyomas, which are of particular concern in differentiating GCTs, appear as a similarly hypoechoic and margined mass on EUS.[1] GCTs, however, are more echogenic and display posterior

shadowing.[1] However, reliably differentiating lesions in the mucosa and muscularis propria with EUS and endoscopy alone may be difficult, and definitive diagnosis relies on tissue histopathologic examination and IHC.

EUS or computed tomography–guided fine-needle biopsies are the preferred methods of biopsy with histology characteristically revealing nests or sheets of polygonal or fusiform cells with abundant eosinophilic or granular amphophilic cytoplasm, a consequence of enlarged lysosomes.[1,3] Cells are characterized by small, pyknotic nuclei.[1] However, some studies discourage biopsy because of the risks of bleeding, ulceration, infection, fistula formation, and misdiagnosis when pseudoepithelial hyperplasia overlies submucosal granular tumors, which mimics squamous cell carcinoma.[4,5]

IHC plays an important role in the diagnosis of GCTs. Complete workup includes Melan-A, smooth muscle actin (SMA), CD34, CD31, CD68, HMB-45, cytokeratin, and S100.[2] Recent studies recommend additional staining with p53 and Ki-67, as malignant tumors often express increased Ki-67 staining.[2,4,7] The role of p53 is less certain than the role of Ki-67, as the literature has failed to demonstrate a significant difference with regard to p53 expression and tumor classification as benign, atypical, or malignant.[2,4] Consistent with a neurogenic origin, esophageal GCTs are diastase resistant and frequently stain positively for periodic acid–Schiff, nestin, S100, and CD68.[1,3,6] GCTs are generally negative for SMA, desmin, CD117, and CD34.[1] Unlike GCTs, esophageal leiomyomas are positive for both SMA and desmin but generally negative for S100.[5] Although melanomas and malignant schwannomas are S100 positive, they are often additionally positive for both HMB-45 and vimentin. IHC of our patient revealed similar findings, demonstrating S100 and CD68 positivity with negativity for actin and CD117.

Malignant esophageal GCTs are exceptionally rare with $<$40 cases identified in the literature and accounting for only 2% of cases.[2,4] Although no racial predisposition for benign tumors is apparent, one study found that malignant GCTs most frequently occurred in African American women vs any other population.[2] The same study further reported malignant GCTs as most commonly occurring in the soft tissues of the thigh vs the head and neck region for benign tumors.[2] Unlike the more common GCTs of the tongue and skin, those of the esophagus often lack significant malignant potential.[1]

The classification of esophageal GCTs as benign or malignant remains poorly defined. Nevertheless, identifying any malignant features is important because of the potentially aggressive features and dismal prognosis associated with metastatic disease. In 1998, Fanburg-Smith et al[7] suggested 6 histologic criteria for distinguishing benign from atypical or malignant tumors.[2] The Fanburg-Smith histologic criteria generated a 3-tier system for malignant classification defined by the following characteristics: increased nuclear-cytoplasmic ratio, nuclear pleomorphism, vesicular nuclei with prominent nucleoli, tumor necrosis, spindling, and increased mitotic activity ($>$2/high-power field).[1-3,7] Neoplasms with $\geq$3 criteria are considered malignant, while those meeting 1-2 criteria are classified as atypical.[1,3,7] Those meeting 0 criteria are benign. Because spindling was present in the pathologic process observed in our patient, we classified his esophageal GCT as atypical. However, intraobserver reliability is variable with low reproducibility for both nuclear pleomorphism and nuclear-cytoplasmic ratio.[1] Additionally, the presence of necrosis and/or increased mitotic activity has repeatedly been the strongest and most reproducible correlator of malignant potential.[2] Based on the Fanburg-Smith criteria,[7] the pathologic profile of our patient's GCT was considered benign.

In the study of 28 malignant GCTs by Fanburg-Smith et al,[7] 39% of patients died from disease-related complications at 3 years. In a 2-year period, they found that 50% of patients had metastases, and 32% experienced local recurrence. Only 32% were disease free at 7 years. Malignant tumors tend to be $>$4 cm and to exhibit rapid growth and/or rapid recurrence after local excision.[7] The median diameter of metastasizing tumors was 5.5 cm vs a median of 2.2 cm in nonmetastasizing tumors.[7] Additionally, Fanburg-Smith et al[7] concluded that certain factors were associated with a poorer prognosis: local recurrence, metastases, larger tumor size, patient age, and histologic features of malignancy. Still, each individual characteristic does not share equal prognostic weight. That is, the absence of increased mitotic activity does not guarantee a benign clinical course and vice versa.

In recent years, EUS has become invaluable in guiding treatment options. Small, asymptomatic esophageal GCTs ($<$10 mm in diameter) should be treated conservatively.[5] As such, small, asymptomatic esophageal GCTs require yearly surveillance with endoscopy and EUS to monitor growth, recurrence, or malignant transformation. Some authors[3] recommend histologic evaluation every 1-2 years, especially for patients with atypical or concerning features.

Endoscopic or surgical removal is recommended for lesions that are $>$10 mm, symptomatic, or exhibit rapid growth, suspicion of malignancy, or infiltration.[5] Endoscopic mucosal resection (EMR) or submucosal tunneling endoscopic resection (STER), a variation of endoscopic submucosal dissection, is preferred to traditional open resection.[1,5] EMR is well tolerated in patients with lesions $\leq$20 mm in diameter and no underlying attachment to the muscularis propria.[5] STER is a newer technique that is preferred for lesions 20-30 mm in diameter or lesions located within the submucosa but not within the muscularis propria.[5] Aside from its advantages in resection of larger neoplasms, STER has the added benefits of providing direct endoscopic visualization and maintenance of the GI tract, promoting wound healing, and decreasing secondary infection and the risk of esophageal perforation.[5,8] In fact, recent literature (2014, 2015) recommends the use of STER because it allows an accurate resection that is safe and less invasive than traditional techniques such as surgical resection while remaining cost effective.[1,8] Important to consider, however, is that STER is only suitable for patients able to tolerate anesthesia with endotracheal intubation because it is performed under general anesthesia.[8] Nevertheless, risks of complications such as bleeding, infection, mediastinitis, abscess, or stricture formation must be addressed.[3]

Video-assisted thoracoscopic surgery and traditional open surgery are the most invasive management options and are reserved for the largest and most complicated malignant lesions.[5] Although not routinely recommended, thoracoscopic surgery and traditional open surgery are specifically indicated for malignancy, deep layer invasion, and multiple symptoms or for patients with a contraindica-

tion to endoscopic surgery.[5] Still, surgical excision has shown good outcomes in the literature, with studies reporting only 8% tumor recurrence.[3] The use of chemotherapy and/or radiation as adjuvant therapy has generally been poor and unfavorable.[2]

CONCLUSION

Esophageal GCTs are uncommon tumors of the GI tract that are often diagnosed incidentally in middle-aged patients. The utility of EUS is invaluable for determining lesion size, origin, borders, and echogenic structure. Although GCTs are typically asymptomatic with an insidious clinical course, approximately 2% of GCTs are malignant upon histopathologic examination. Endoscopic resection is considered a safe and effective therapeutic option for esophageal GCTs because of the poor prognosis of metastatic disease and morbidity associated with large tumors.

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